PATENT APPLICATION TRANSMITTAL (Conty for new nonprovisional applications under 37 CFR 1.53(h)) APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents. 1. Fee Transmitted Form (e.g., PTO/SB/17) (Submit as originated and application by the processing) Applicant claims small entilly status. See 37 CFR 1.27. 3. Specification [Total Pages 152] (Inviered arrangement ast forth below) - Described the of the Invention - Cross Reterence to Roberd Applications - Statement Regarding fived apparentle - Background of the Invention - Bied Description of the Drewings (Filled) - Description of the Drewings (F		eduction Act of 1985, no persons are require			
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AMENDMENTS TO THE CLAIMS

- 1. (cancelled)
- 2. (currently amended) The composition of Claim [[1]] 56 wherein R¹ is selected from:
 - (A) aryl;
- (B) substituted aryl, wherein the substituents on said substitued aryl are selected from: (1) halo; or (2) alkyl; or (3) substituted alkyl;
 - (C) heteroaryl;
 - (D) substituted heteroaryl; or
 - (E) when R¹ is taken together with X, then the moiety is

- 3. (currently amended) The compound composition of Claim 2 wherein R¹ is selected from:
 - (A) phenyl;
- (B) substituted phenyl wherein the substituents on said substitued phenyl are selected from: (1) halo; (2) alkyl; (3) alkyl substituted with halo;
- (C) heteroaryl selected from: pyridyl, thienyl, pyrimidinyl, thiazolyl or pyridyl N-Oxide;
 - (D) alkyl substituted thiazolyl; or
 - (E) when R¹ is taken together with X, then the moiety is

wherein c is 0 or 1, and when c is 1 then R⁶ is halo.

- 4. (currently amended) The compound composition of Claim 3 wherein R¹ is selected from:
 - (A) phenyl;

- (B) substituted phenyl, wherein the substituents on said substitued phenyl are independently selected from: chloro, fluoro or trifluoromethyl;
 - (C) heteroaryl selected from:

(D) substituted heteroaryl of the formula:

(E) when R¹ is taken together with X, then the moiety is

wherein c is 0 or 1, and when c is 1 then R⁶ is fluoro.

- 5. (currently amended) The compound composition of Claim [[1]] 56 wherein R¹ is selected from:
 - (A) phenyl;
- (B) substituted phenyl, wherein the substituents on said substitued phenyl are independently selected from: chloro, fluoro or trifluoromethyl;
 - (C) pyridyl; or
 - (D) substituted heteroaryl of the formula:

(E) when R¹ is taken together with X, then the moiety is

wherein c is 0 or 1, and when c is 1 then R^6 is fluoro.

- 6. (currently amended) The composition of Claim 5 wherein R¹ is pyridyl.
 - 7. (currently amended) The compound composition of Claim 6 wherein R¹ is



- 8. (currently amended) The compound composition of Claim [[1]] $\underline{56}$ wherein X is =C(NOR³), and R³ is selected from H or alkyl.
- 9. (currently amended) The compound composition of Claim 8 wherein R³ is selected from H, methyl or ethyl.
- 10. (currently amended) The composition of Claim 9 wherein R³ is methyl.
- 11. (currently amended) The compound composition of claim [[1]] <u>56</u> wherein: (1) M² is nitrogen; and (2) M³ and M⁴ are selected such that: (a) one is carbon and the other is nitrogen, or (b) both are nitrogen.
- 12. (currently amended) The $\frac{1}{1}$ composition of Claim 11 wherein M^3 is carbon, and M^4 is nitrogen.
- 13. (currently amended) The composition of Claim [[1]] 56 wherein:

n is 2;.

a is 0 or 1;

b is 0 or 1:

c is 0 or 1, and when c is 1 then R⁶ is halo;

e is 1 to 5; and

p is 2.

- 14. (currently amended) The compound composition of claim [[1]] 56 wherein Y is =C(O).
- 15. (currently amended) The composition of Claim [[1]] $\underline{56}$ wherein Z is C₁ to C₃ alkyl.
- 16. (currently amended) The compound composition of Claim [[1]] 56 wherein Z is

$$-CH_2-$$
 or $-CH_3$

- 17. (currently amended) The composition of Claim [[1]] 56 wherein R² is a six membered heteroaryl ring.
- 18. (currently amended) The compound composition of Claim 17 wherein R² is selected from pyridyl, pyridyl substituted with –NR⁴R⁵, pyrimidinyl, or pyrimidinyl substituted with –NR⁴R⁵.
- 19. (currently amended) The compound composition of Claim 18 wherein R² is pyridyl substituted with –NH₂, or pyrimidinyl substituted with –NH₂.
- 20. (currently amended) The compound composition of Claim 19 wherein R² is

21. (currently amended) The compound composition of Claim [[1]] $\underline{56}$ wherein R^4 is H or lower alkyl; R^5 is H, C_1 to C_6 alkyl, or $-C(O)R^4$; R^{12} is alkyl, hydroxy or fluoro; and R^{13} is alkyl, hydroxy or fluoro.

- 22. (currently amended) The compound composition of Claim 21 wherein R⁴ is H or methyl; R⁵ is H or methyl; R¹² is hydroxy or fluoro; and R¹³ is hydroxy or fluoro.
- 23. (currently amended) The compound <u>composition</u> of Claim [[1]] <u>56</u> wherein:
 - (1) R¹ is selected from:
 - (A) aryl;
- (B) substituted aryl, wherein the substituents on said substitued aryl are selected from: (1) halo; or (2) alkyl; or (3) substituted alkyl;
 - (C) heteroaryl; or
 - (D) substituted heteroaryl; or
 - (E) when R¹ is taken together with X, then the moiety is

- (2) $X \text{ is } = C(NOR^3);$
- (3) R³ is selected from H or alkyl;
- (4) M² is nitrogen;
- (5) Y is =C(O);
- (6) M³ and M⁴ are selected such that: (1) one is carbon and the other is nitrogen, or (2) both are nitrogen;
 - (7) Z is C_1 to C_3 alkyl; and
 - (8) R² is a six membered heteroaryl ring.
 - 24. (currently amended) The compound composition of Claim 23 wherein:
 - (1) R¹ is selected from:
 - (A) phenyl;
- (B) substituted phenyl wherein the substituents on said substitued phenyl are selected from: (1) halo; (2) alkyl; (3) alkyl substituted with halo;
- (C) heteroaryl selected from: pyridyl, thienyl, pyrimidinyl, thiazolyl or pyridyl N-Oxide; or
 - (D) alkyl substituted thiazolyl; or

(E) when R¹ is taken together with X, then the moiety is

wherein c is 0 or 1, and when c is 1 then R⁶ is halo;

- (2) R³ is selected from H, methyl or ethyl;
- (3) n is 2,
- (4) a is 0 or 1,
- (5) b is 0 or 1,
- (6) c is 0 or 1 and when c is 1 then R⁶ is halo,
- (7) e is 1 to 5,
- (8) p is 2,
- (9) R⁴ is H or lower alkyl,
- (10) R^5 is H, C₁ to C₆alkyl, or -C(O) R^4 ;
- (11) R¹² is alkyl, hydroxy or fluoro, and
- (12) R¹³ is alkyl, hydroxy or fluoro.
- 25. (currently amended) The compound composition of Claim 24 wherein ${\sf R}^2$ is

R¹ is

M² is nitrogen, M³ is carbon, and M⁴ is nitrogen.

26 to 43. (cancelled)

- 44. (currently amended) The method of Claim [[43]] <u>57</u> wherein said H₁ receptor antagonist is selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.
- 45. (original) The method of Claim 44 wherein said H₁ receptor antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine or cetirizine.
- 46. (original) The method of Claim 45 wherein said H₁ receptor antagonist is selected from: loratadine or descarboethoxyloratadine.

47 to 50. (cancelled)

51. (currently amended) A pharmaceutical composition comprising an effective amount of a compound of Claim 1 of Claim 56, and an effective amount of H₁-receptor antagonist, and a pharmaceutically effective carrier, wherein said compound of Claim 1 formula I is selected from:

52. (currently amended) A method of treating: allergy, allergy induced airway responses, and congestion comprising administering to a patient in need of such treatment an effective amount of a compound of Claim 1 in combination with an effective amount of an H₁ receptor antagonist, Claim 57 wherein said compound of Claim 1 formula I is selected from:

; or

- 53. (original) The method of Claim 52 wherein said H₁ receptor antagonist is selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.
- 54. (original) The method of Claim 53 wherein said H₁ receptor antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine or cetirizine.
- 55. (original) The method of Claim 54 wherein said H₁ receptor antagonist is selected from: loratedine or descarboethoxyloratedine.
- 56. (new) A pharmaceutical composition comprising an effective amount of a compound of the formula I:

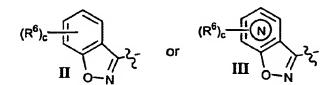
or a pharmaceutically acceptable salt or solvate thereof, wherein:

- (1) R¹ is is selected from:
 - (a) aryl;
 - (b) heteroaryl;

- (c) heterocycloalkyl
- (d) alkyl;
- (e) cycloalkyl; or
- (f) alkylaryl;

wherein said R¹ groups are optionally substituted with 1 to 4 substituents independently selected from:

- (1) halogen;
- (2) hydroxyl;
- (3) lower alkoxy;
- (4) -CF₃;
- (5) CF₃O-;
- (6) -NR⁴R⁵;
- (7) phenyl;
- (8) -NO₂,
- (9) -CO₂R⁴;
- (10) -CON(R4)2 wherein each R4 is the same or different;
- (11) -S(O)_mN(R²⁰)₂ wherein each R²⁰ is the same or different H or alkyl group;
- (12) -CN; or
- (13) alkyl; or
- (2) R¹ and X taken together form a group selected from:



wherein N represents a nitrogen atom located at one of the 4 non-fused positions of the ring;

(3) X is selected from: =C(O), $=C(NOR^3)$, $=C(NNR^4R^5)$,

- (4) M¹ is carbon;
- (5) M^2 is selected from C or N;

- (6) M³ and M⁴ are independently selected from C or N;
- (7) Y is selected from: is $-CH_{2-}$, =C(O), $=C(NOR^{20})$ (wherein R^{20} is as defined above), or =C(S);
 - (8) Z is a $C_1 C_6$ alkyl group;
- (9) R² is a five or six-membered heteroaryl ring, said six-membered heteroaryl ring comprising 1 or 2 nitrogen atoms with the remaining ring atoms being carbon, and said five-membered heteroaryl ring containing 1 or 2 heteroatoms selected from: nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; said five or six membered heteroaryl rings being optionally substituted with 1 to 3 substituents independently selected from: halogen, hydroxyl, lower alkyl, lower alkoxy, -CF₃, CF₃O-, -NR⁴R⁵, phenyl, -NO₂, -CO₂R⁴, -CON(R⁴)₂ wherein each R⁴ is the same or different, -CH₂NR⁴R⁵, -(N)C(NR⁴R⁵)₂, or -CN;
 - (10) R³ is selected from:
 - (a) hydrogen;
 - (b) $C_1 C_6$ alkyl;
 - (c) aryl;
 - (d) heteroaryl;
 - (e) heterocycloalkyl;
 - (f) arylalkyl;
 - (g) -(CH₂)_e-C(O)N(R⁴)₂ wherein each R⁴ is the same or different,
 - (h) -(CH₂)_e-C(O)OR⁴;
 - (i) -(CH₂)_e-C(O)R³⁰ wherein R³⁰ is a heterocycloalkyl group, or

- (j) -CF₃; or
- (k) -CH₂CF₃;

wherein said aryl, heteroaryl, heterocycloalkyl, and the aryl portion of said arylalkyl are optionally substituted with 1 to 3 substituents selected from: halogen, -OH, -OCF₃, -CF₃, -CN, -N(R^{45})₂, -CO₂ R^{45} , or -C(O)N(R^{45})₂, wherein each R^{45} is independently selected from: H, alkyl, alkylaryl, or alkylaryl wherein said aryl moiety is substituted with 1 to 3 substituents independently selected from -CF₃, -OH, halogen, alkyl, -NO₂, or -CN;

- (11) R^4 is selected from: hydrogen, $C_1 C_6$ alkyl, aryl, alkylaryl, said aryl and alkylaryl groups being optionally substituted with 1 to 3 substituents selected from: halogen, $-CF_3$, $-OCF_3$, -OH, $-N(R^{45})_2$, $-CO_2R^{45}$, $-C(O)N(R^{45})_2$, or -CN; wherein R^{45} is as defined above;
- (12) R^5 is selected from: hydrogen, $C_1 C_6$ alkyl, $-C(O)R^4$, $-C(O)_2R^4$, or $-C(O)N(R^4)_2$ wherein each R^4 is independently selected, and R^4 is as defined above;
- (13) or R⁴ and R⁵ taken together with the nitrogen atom to which they are bound forms a five or six membered heterocycloalkyl ring;
- (14) R⁶ is selected from: alkyl, aryl, alkylaryl, halogen, hydroxyl, lower alkoxy, -CF₃, CF₃O-, -NR⁴R⁵, -NO₂, -CO₂R⁴, -CON(R⁴)₂ wherein each R⁴ is the same or different, or -CN;
 - (15) R¹² is selected from: alkyl, hydroxyl, alkoxy, or fluoro;
 - (16) R¹³ is selected from: alkyl, hydroxyl, alkoxy, or fluoro;
 - (17) a is 0 to 2:
 - (18) b is 0 to 2;
 - (19) c is 0 to 2;
 - (20) e is 0 to 5;
 - (21) m is 1 or 2;
 - (22) n is 1, 2 or 3; and
- (23) p is 1, 2 or 3, with the proviso that when M^3 and M^4 are both nitrogen, then p is 2 or 3;

and an effective amount of H₁ receptor antagonist, and a pharmaceutically effective carrier.

57. (new) A method of treating: allergy, allergy-induced airway responses, and congestion comprising administering to a patient in need of such treatment an effective amount of a compound of formula I:

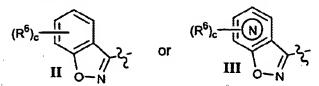
$$R^{1}$$
 $X^{-M^{1}}$
 M^{2}
 M^{3}
 M^{4}
 Z
 R^{2}
 (I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

- (1) R¹ is is selected from:
 - (a) aryl;
 - (b) heteroaryl;
 - (c) heterocycloalkyl
 - (d) alkyl;
 - (e) cycloalkyl; or
 - (f) alkylaryl;

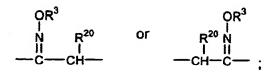
wherein said R¹ groups are optionally substituted with 1 to 4 substituents independently selected from:

- (1) halogen;
- (2) hydroxyl;
- (3) lower alkoxy;
- (4) -CF₃;
- (5) CF₃O-;
- (6) -NR⁴R⁵;
- (7) phenyl;
- (8) -NO₂,
- (9) -CO₂R⁴;
- (10) -CON(R4)2 wherein each R4 is the same or different;
- (11) -S(O)_mN(R²⁰)₂ wherein each R²⁰ is the same or different H or alkyl group;
- (12) -CN; or
- (13) alkyl; or
- (2) R¹ and X taken together form a group selected from:



wherein (N) represents a nitrogen atom located at one of the 4 non-fused positions of the ring;

(3) X is selected from: =C(O), $=C(NOR^3)$, $=C(NNR^4R^5)$,



- (4) M¹ is carbon;
- (5) M² is selected from C or N;
- (6) M³ and M⁴ are independently selected from C or N;
- (7) Y is selected from: is $-CH_{2^-}$, =C(O), $=C(NOR^{20})$ (wherein R^{20} is as defined above), or =C(S);
 - (8) Z is a $C_1 C_6$ alkyl group;
- (9) R² is a five or six-membered heteroaryl ring, said six-membered heteroaryl ring comprising 1 or 2 nitrogen atoms with the remaining ring atoms being carbon, and said five-membered heteroaryl ring containing 1 or 2 heteroatoms selected from: nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; said five or six membered heteroaryl rings being optionally substituted with 1 to 3 substituents independently selected from: halogen, hydroxyl, lower alkyl, lower alkoxy, -CF₃, CF₃O-, -NR⁴R⁵, phenyl, -NO₂, -CO₂R⁴, -CON(R⁴)₂ wherein each R⁴ is the same or different, -CH₂NR⁴R⁵, -(N)C(NR⁴R⁵)₂, or -CN;
 - (10) R³ is selected from:
 - (a) hydrogen;
 - (b) $C_1 C_6$ alkyl;
 - (c) aryl;
 - (d) heteroaryl;
 - (e) heterocycloalkyl;
 - (f) arylalkyl;
 - (g) -(CH₂)_e-C(O)N(R⁴)₂ wherein each R⁴ is the same or different,
 - (h) $-(CH_2)_e-C(O)OR^4$;
 - (i) -(CH₂)_e-C(O)R³⁰ wherein R³⁰ is a heterocycloalkyl group, or

- (j) -CF₃; or
- (k) -CH₂CF₃;

wherein said aryl, heteroaryl, heterocycloalkyl, and the aryl portion of said arylalkyl are optionally substituted with 1 to 3 substituents selected from:

halogen, -OH, -OCF₃, -CF₃, -CN, -N(\mathbb{R}^{45})₂, -CO₂ \mathbb{R}^{45} , or -C(O)N(\mathbb{R}^{45})₂, wherein each \mathbb{R}^{45} is independently selected from: H, alkyl, alkylaryl, or alkylaryl wherein said aryl moiety is substituted with 1 to 3 substituents independently selected from -CF₃, -OH, halogen, alkyl, -NO₂, or -CN;

- (11) R^4 is selected from: hydrogen, $C_1 C_6$ alkyl, aryl, alkylaryl, said aryl and alkylaryl groups being optionally substituted with 1 to 3 substituents selected from: halogen, $-CF_3$, $-OCF_3$, -OH, $-N(R^{45})_2$, $-CO_2R^{45}$, $-C(O)N(R^{45})_2$, or -CN; wherein R^{45} is as defined above;
- (12) R^5 is selected from: hydrogen, $C_1 C_6$ alkyl, $-C(O)R^4$, $-C(O)_2R^4$, or $-C(O)N(R^4)_2$ wherein each R^4 is independently selected, and R^4 is as defined above;
- (13) or R⁴ and R⁵ taken together with the nitrogen atom to which they are bound forms a five or six membered heterocycloalkyl ring;
- (14) R⁶ is selected from: alkyl, aryl, alkylaryl, halogen, hydroxyl, lower alkoxy, -CF₃, CF₃O-, -NR⁴R⁵, -NO₂, -CO₂R⁴, -CON(R⁴)₂ wherein each R⁴ is the same or different, or -CN;
 - (15) R¹² is selected from: alkyl, hydroxyl, alkoxy, or fluoro;
 - (16) R¹³ is selected from: alkyl, hydroxyl, alkoxy, or fluoro;
 - (17) a is 0 to 2;
 - (18) b is 0 to 2;
 - (19) c is 0 to 2;
 - (20) e is 0 to 5;
 - (21) m is 1 or 2;
 - (22) n is 1, 2 or 3; and
- (23) p is 1, 2 or 3, with the proviso that when M^3 and M^4 are both nitrogen, then p is 2 or 3;

in combination with an effective amount of an H_1 receptor antagonist.

58. (new) A pharmaceutical composition comprising an effective amount of a compound of the formula

and an effective amount of H₁ receptor antagonist, and a pharmaceutically effective carrier.

- 59. (new) The composition of claim 58 wherein the H₁ receptor antagonist is selected from loratedine or descarboethoxyloratedine.
- 60. (new) A method of treating: allergy, allergy-induced airway responses, and congestion comprising administering to a patient in need of such treatment an effective amount of a compound of the formula

in combination with an effective amount of an H₁ receptor antagonist.

61. (new) The method of claim 60 wherein the H_1 receptor antagonist is selected from loratedine or descarboethoxyloratedine.